HARVARD MEDICAL SCHOOL
THE DEPARTMENT OF PHARMACOLOGY
25 SHATTUCK ST., BOSTON 15, MASS.

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Dr. Joshua Lederberg
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Dear Joshua:

I am sorry you cannot participate in the panel discussion, and puzzled at your question what I have in mind as the connection between this topic (transduction) and the biochemical basis of acquired (?) resistance. By acquired resistance I mean the development of resistance in a cell that was not previously resistant. This is meant to narrow the scope by excluding from primary consideration the enormous question why some cells are more sensitive to drugs than others, a question that is really the whole problem of drug selectivity. That would be too much.

By biochemical I mean the molecular basis of the changed resistance of the cell, insofar as it can be intelligently discussed at this time. I mean also to direct attention and emphasis to the idea that the genetic changes are controlling (very likely) the macromolecular systems interacting with drugs, but the genetic material is usually not itself interacting with drug-- i.e. the fundamental change in the cell, which makes it drug-resistant, is to be explained in biochemical terms, although it came about through a genetic mechanism.

I did not ask you to discuss transduction. I asked for a discussion of "directed heritable transformations". Whether the transformations to drug-resistance are related to transduction, and in what way, is something I am ignorant about, but hope to learn about from whomever I can persuade to discuss this topic.

I am glad to see that an aspect of pharmacology has caught your fancy. The literature is poor and scanty beyond that the organism becomes able to tolerate many lethal doses of a variety of drugs after continued exposure to them. Morphine has been best studied, but poorly, and it is only within the last few years that we know for certain that enormous morphine concentrations circulate in the blood of tolerant animals-- i.e. that the phenomenon is a change at the cellular level. Nicotine is a classic example. A rapidly developing tolerance called by the fancy name tachyphylaxis can be demonstrated in isolated smooth muscle with drugs like ephedrine. I don't know of any case in which mechanism has been demonstrated.

At Washington last year there was a symposium organized by Sevag that tried to put all these questions of changed responses to chemicals into one basket but it turned out to be an indigestible omelet and I want to steer clear of it. Thanks anyway.

Sincerely,

Avram Goldstein